Title

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Impact of Hepatitis B Core Antibody (HBcAb) Seropositivity on the Outcome of High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma

Muzaffar H. Qazilbash, MD

Abstract

Background—Hepatitis B core antibody (HBcAb) seropositivity has been associated with a higher rate of hepatitis B virus (HBV) reactivation after chemotherapy, even in patients who are hepatitis B surface antigen (HBsAg) negative. We evaluated the incidence of hepatitis B reactivation and liver toxicity in patients with multiple myeloma (MM) who received high-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (auto-HCT) at our institution.

Methods—We identified 107 MM patients with resolved HBV infection (HBcAb positive, HBsAg negative) and 125 patients with negative HBV serology (control) who were matched for age, time of auto-HCT, disease status and preparative regimen. Both groups received HDC and auto-HCT between 1991 and 2013. Primary endpoints were: 1) HBV reactivation defined as HBsAg positivity or ≥10-fold increase in HBV DNA; 2) hepatotoxicity, as defined in NCI CTCv3.0.

Results—Approximately 70% in each group received melphalan alone as preparative regimen. In the resolved HBV infection group, 52 patients (49%) were Hepatitis B surface antibody (HBsAb) positive, and 24 (22%) had detectable HBV DNA prior to auto-HCT. Serum HBV DNA level was <100 IU/m in 22 patients, and <300 IU/ml in 2 patients. Hepatitis B e antigen (HBeAg) was non-reactive in all 4 patients evaluated prior to auto-HCT. Only 1 patient with resolved HBV infection received pre-emptive antiviral therapy with Lamivudine, while 4 patients received Lamivudine (3) or Tenofovir (1) at reactivation for a median duration of 1 year. HBV reactivation was seen in 7 of 107 (6.5%) patients in the resolved HBV group. There was a ≥10-fold increase in HBV DNA in 5 of 7 patients with HBV reactivation, and 2 of 7 also became positive for HBeAg. Median time to HBV reactivation from auto-HCT was 16 months. The cumulative incidence of grade 2 or more hepatotoxicity in resolved HBV infection and the control groups was 30% and 22%, respectively (hazard ratio [HR] 1.3; 95% confidence interval [CI], 0.7–2.3; $P = 0.4$). There was a trend for higher NRM in the control group at 1 year 7% vs 1%, with a HR of 0.15 (95% CI 0.02–1.2, $P = 0.08$) and at 2 years 8% vs 1% with a HR of 0.13 (95% CI 0.02–1.1, $P = 0.06$) after auto-HCT. With a median follow up of 18 and 35 months in resolved HBV infection vs. control groups, the median progression free survival was 21 and 18 months (p=0.5), respectively. Median overall survival in resolved HBV infection and control groups was 53 vs. 67 months (p=0.2), respectively.

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Conflict of Interest: The authors have no conflict of interest.

Conclusion—Resolved HBV infection is associated with a significant risk of HBV reactivation and hepatotoxicity in patients undergoing auto-HCT for MM. These complications were reversible and were not associated with a decrease in PFS or OS.

INTRODUCTION

Hepatitis B Virus (HBV) infection is a global disease with an estimated 240 million people infected worldwide with chronic hepatitis B[1]. Center for Disease Control and Prevention estimates that there are 700,000– 1.4 million people infected with chronic HBV infection in United States[2]. The spectrum of HBV related diseases is varied and includes acute infection, chronic infection, inactive carrier state, resolved infection, and reactivation of HBV.

Reactivation of HBV is a well-recognized complication in patients undergoing high dose chemotherapy and hematopoietic stem transplants[3–6]. It can have varied manifestation, from being asymptomatic to spontaneous resolution to acute hepatitis flare. Severe acute hepatitis flare can sometime progress to fulminant hepatic failure and death[7,8]. Reactivation of HBV occurs in two distinct populations: a) the chronic/inactive hepatitis B surface antigen (HbsAg) carriers and b) those with resolved HBV infection (positive Hepatitis B core antibody [HBcAb] and negative for HbsAg), in whom the virus has apparently been cleared (reverse seroconversion). Approximately 95% of the adults infected with HBV successfully clear the virus, serologically manifested as disappearance of the HbsAg and persistence of HBcAb and Hepatitis B surface antibodies (HbsAb)[9]. The serological clearance of HBsAg increases with age, with the annual HBsAg sero-clearance rate being 1.05–1.61% after 50 years of age[10]. Despite serological clearance of the HBV virus, it can persist for decades in a dormant or low replicative state in the liver and circulating blood[11,12]. Replication of the dormant virus, enhanced with immunosuppressive therapy is thought to cause the reactivation in the resolved HBV group.

To date, several studies have reported reactivation of HBV in chronic HBV carriers[3,5,13], but very few in those with resolved infection, and even those are limited to non-transplant population[14,15]. Limited series in resolved HBV group have reported a wide range of reactivation varying from 6–86%[16–19]. A recent retrospective study at our institution reported an incidence of HBV reactivation among hematological malignancy patients of 11.6% after allogeneic HCT[20].

The prevalence of HBV infection in multiple myeloma (MM) patients ranges from 6–19 %[21–23], but the prevalence of resolved HBV infection prior to auto-HCT (autologous hematopoietic stem cell transplantation) and the frequency of reverse seroconversion after auto-HCT is unclear. The effect of resolved HBV infection in MM patients post auto-HCT has not been reported to date. We performed this retrospective study, with the primary aim to evaluate the impact of resolved HBV infection on the outcome of high dose chemotherapy and auto- HCT for MM patients. Our secondary aim was to determine the prevalence of resolved HBV infection, the incidence of reactivation and liver toxicity in these patients.

Methods

We conducted a retrospective study in MM patients who received auto-HCT at the University of Texas MD Anderson Cancer from August 1991 to March 2013. The study was approved by the Institutional Review Board at MD Anderson Cancer Center. A total of 1345 MM patients had auto-HCT during this time and 107 patients (8%) had evidence of resolved hepatitis B infection, which was defined as HBcAb +ve and HBsAg −ve. We electronically identified 125 MM patients transplanted at the same time with negative HBV serology as controls, who were matched to the cases with respect to age, time of auto- HCT, disease status at transplant and the preparative regimen.

Commercially available enzymes immunoassay kits were used for the detection of HbsAg, HBsAb, HBcAb and Hepatitis B e antigen (HBeAg). HBV DNA was detected and quantified by nucleic acid hybridization or branched DNA amplification by an outside reference laboratory. Data regarding patient demographics, pre transplantation disease status, conditioning regimen, and post transplantation outcome and course were obtained from the departmental data base. The clinical database and electronic medical records were extensively searched to collect detailed information on liver function tests, HBV serology, viral load and HBV treatment. All patients had liver function tests (baseline liver function) before the start of preparative regimen. Post auto-HCT, patients were followed in the clinic at an interval of 3–6 months and during each visit they had their liver functions tests repeated. HBV serology was not repeated in all patients post-transplant except for those who had abnormal transaminase level post auto-HCT. Patients were also evaluated for clinical signs of cirrhosis, hepatic encephalopathy and ascites during their clinic visits by their physicians.

Endpoints

Primary endpoints were: 1) HBV reactivation defined as HBsAg positivity or ≥10-fold increase in HBV DNA; 2) hepatotoxicity, as defined in NCI CTCv3.0. The secondary end points were veno-occlusive disease (VOD), treatment-related mortality, progression-free survival (PFS) and overall survival (OS). HBV reactivation was defined as reappearance of HbsAg or a 10 fold increase in HBV DNA post auto-HCT compared to the pre-transplant state[24,25]. Hepatotoxicity was defined according to NCI Common Terminology Criteria for Adverse Events version 3.0 (NCI CTC v3.0) (grade 0, none; grade 1, >ULN–1.5 × ULN; grade 2, >1.5 –3.0 × ULN; grade 3, >3.0–10.0 × ULN; and grade 4, >10.0 ·ULN for bilirubin, and grade 0, none; grade 1, >ULN–2.5 × ULN; grade 2, >2.5 –5.0 × ULN; grade 3, 5.0–20.0 × ULN; and grade 4, >20 × ULN). Peak values of aminotransferase, alkaline phosphatase, and total bilirubin were recorded for each patient in the resolved hepatitis group and the control group within one year of auto-HCT. Veno-occlusive disease of the liver was defined as total bilirubin level greater than 2mg/dl within 21 days of transplantation with any two of the following: hepatomegaly, ascites, weight gain more than 5% from the pre transplant weight[26] and no other explanation for these findings[27]. Fulminant hepatic failure was described as the development of encephalopathy within 2 weeks of the onset of jaundice[28].

Statistical Methods

Patient characteristics were compared using chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. The incidence rates of HBV reactivation and hepatotoxicity were estimated using the cumulative incidence method considering death before the event of interest as a competing risk. OS and PFS were estimated using the Kaplan-Meier method. Cox proportional hazards regression analysis was used to compare outcomes between HBV cases and controls. It was also used to assess predictors of OS on univariable and multivariable analysis.. The impact of HBV reactivation on OS was assessed by considering reactivation as a time dependent variable. Statistical significance was defined at the 0.05 level. Statistical analysis was primarily performed using Stata11 software (Stata Corp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: Stata Corp LP)

RESULTS

Baseline patient characteristics

The baseline characteristics of the MM patients with the resolved HBV infection and the control group are listed in table 1. The median age of the patients in the resolved HBV infection and control groups was 58 (range 31–74) and 58 (range 34–75) years, respectively. Resolved HBV group had more patients with age 65 or above, compared to the control group (20% vs 10%, p= 0.05). The two groups were otherwise comparable in serum creatinine at diagnosis, cytogenetics, induction regimen, disease status, and the preparative regimen used. Although the two groups were similar in terms of overall response (>/=PR) prior to auto-HCT, 21% patients in the resolved HBV group had at least achieved a VGPR before auto-HCT, compared to 11% in the control (p=0.06).

Table 2 summarizes the HBV serology for the resolved HBV infection group. All patients were HBcAb +ve. None of them had detectable HbsAg in the serum prior to auto-HCT. Seventy-three patients were tested for HBsAb prior to auto-HCT, and 52 of them (49%) were positive. Pre auto-HCT serum HBV DNA levels was tested in 54 patients (50%) and 24 of them had detectable HBV viral load. Four patients were tested for HBeAg and none of them were positive for HBeAg.

Antiviral therapy for HBV reactivation

Only 1 patient with resolved HBV infection received pre-emptive antiviral therapy (lamivudine) prior to auto- HCT that was continued for 6 months post-transplant. His viral load pre transplant was 288 IU/ml (<300 IU/ml). He had HBV reactivation 265 days post auto-HCT. After auto-HCT, 4 patients were started on antiviral therapy for reactivation of resolved HBV infection with either lamivudine (n =3) or tenofovir (n= 1) and were treated for a median duration of 1 year.

HBV Reactivation

The median follow-up in survivors was 18 months (range, 0.2–136 months) for the resolved HBV infection group and 35 months (range, 0.6–168 months) for the control group. HBV reactivation occurred in 7 patients (6.5%) in the resolved HBV infection group. Median time to HBV reactivation was 16 months (range, 7–47 months). The cumulative incidence of

reactivation at one and two year was 3.5% and 5% respectively. Five of the seven patients also met the reactivation criteria by HBV DNA. Two patients also became seropositive for HBeAg.

Hepatotoxicity

No VOD or fulminant liver failure was observed in either of the two groups. The cumulative incidence of grade 2 or more hepatotoxicity (NCI CTCv3.0) in the resolved HBV group and the control were 30% and 22%, respectively (HR 1.3; 95% CI 0.7–2.3; *P*= 0.4).

Non relapse mortality (NRM) and Survival

NRM after auto-HCT in the resolved HBV and the control group at 1 year was 1% and 7%, respectively, (HR 0.15:95% CI 0.02–1.2, p= 0.08), and at 2 years was 1% and 8%, respectively (HR 0.13: 95% CI 0.02–1.1, p= 0.06). The median PFS was 21 months and 18 months in the resolved HBV and controls groups, respectively (p=0.5). Two-year PFS was 44% (95% CI 33–55) and 40% (95% CI 30–49; HR 0.9: 95% CI 0.6–1.3, p =0.5) in the resolved HBV and controls groups, respectively. Median OS in the resolved HBV group was 53 months and in the control group it was 67 months (p=0.2). Two-year OS in resolved HBV and control groups was 84% and 75%, respectively (HR 0.6: 95% CI 0.3–1.2, p = 0.2) (Table 3).

Predictors of Outcome

On univariable analysis, auto-HCT in first remission (HR 0.3, p = 0.001) melphalan alone as preparative regimen (HR 0.5, p= 0.02) and standard-risk cytogenetics (HR ---- p= 0.001) were associated with a longer OS. A multivariate analysis could not be performed due to small number of patients.

DISCUSSION

In this large retrospective study we report that approximately 8% of the MM patients undergoing auto-HCT at our intuition had resolved HBV infection, and the incidence of HBV reactivation in these patients after auto-HCT was 6.5%. We also showed that MM patients with resolved HBV infection have similar outcomes as HBV seronegative MM patients in terms of ≥ grade 2 hepatotoxicity, NRM and survival post auto-HCT. Overall survival for patients with resolved HBV infection in this study was comparable to the OS reported for patients with MM and without HBV infection, who received auto-HCT.[29,30].

To our knowledge, this is the first and the largest study to report the outcome of MM patients with resolved HBV infection who received an auto-HCT. The risk of HBV reactivation is well described in patients with lymphoma, especially after the use of rituximab (reference). However, for MM there are just a few case reports that described the risk of HBV reactivation after cytotoxic chemotherapy[38,39],[19,40]. In these case reports most patients were receiving steroids, proteasome inhibitors or immunomodulatory agents, and very few had undergone an auto-HCT[38,39,40]. Most of these case reports are from Asia, where HBV infection is endemic in general population. Although there was an HBV reactivation rate of 6.5% in our study, interestingly, we did not see any fulminant liver failure. On careful

review, this observation is consistent with the findings reported in patients with lymphoma who experienced HBV reactivation after rituximab-containing regimens.[14,20,32,15,31],

Ramos et al have reported on the outcome of patients with hematologic malignancies and resolved HBV infection, who received an allogeneic (allo)-HCT at our institution. The cumulative incidence of HBV reactivation in that study was 11.6% (reference). They also compared the outcome to a control group of patients with negative HBV serology, and found no difference in OS, relapse rate, NRM or graft vs. host disease between the two groups[20]. The rate of HBV reactivation in our study is lower (6.5 vs. 11.6%), when compared to the rate after allo-HCT. This difference is probably due to a more profound and prolonged immunosuppression after an allo-HCT[20].

We evaluated patients with resolved HBV infection for HBV DNA before auto-HCT, and identified 24 (22%) with detectable HBV DNA. However, 22/23 patients had <100 IU/ml and were monitored without pre-emptive antiviral therapy. Only one patient, with a viral load of 288 IU/ml, received pre-emptive antiviral therapy with lamivudine. Prophylactic or pre-emptive antiviral therapy is not routinely recommended for patients with resolved HBV infection according to the latest guidelines from the European Association of the Study of Liver (EASL).[34,35]. With this approach, the HBV reactivation rate was low (6.5%), and there was no significant increase in hepatotoxicity, fulminant liver failure or transplant-related mortality in the resolved HBV infection group. We also observed that HBV reactivation tends to occur late after auto-HCT, with a median time to HBV reactivation 16 months. Other groups have reported similar delayed reactivation after chemotherapy.[20,24,36]. This observation highlights two important points: 1) a need for long follow up post auto-HCT to detect reactivation; and 2) short-term antiviral prophylaxis after auto-HCT may not be effective in preventing this late reactivation[35,37]. Based on this observation, monitoring for up to 2 years after auto-HCT for HBV reactivation may be necessary.

Our study had several limitations inherent in retrospective analyses. They include the fact that not all the MM patients were tested for serological markers of HBV reactivation (HBsAg) or HBV DNA after auto-HCT. This may have resulted in underestimation of HBV reactivation. Although the cases and controls were matched, there is still a possibility of selection bias.

In summary, we showed that resolved HBV infection in MM is associated with a low risk of HBV reactivation, which is reversible, does not adversely affect survival, and, therefore, is not a contraindication to auto-HCT.

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Table 1

Baseline patient characteristics

	Case N=107		Control N=125		*P**
Days, diagnosis to auto-HCT, median (range)	**9**	(2–161)	**9**	(2–184)	0.98
Age, median (range)	**58**	(31–74)	**58**	(34–75)	
>=65 yrs	21	20%	13	10%	0.05
Creatinine at diagnosis>2mg/dl					
Yes	15	14%	13	10%	0.4
No	70	65%	85	68%	
Unknown	22	21%	27	22%	
Cytogenetic risk					
High	10	9%	14	11%	0.6
Standard	77	72%	88	70%	
Unknown	20	19%	23	18%	
Induction					
IMiD/Dex	26	24%	36	29%	
Bortezomib/IMiD/Dexamethasone	9	8%	13	10%	
Bortezomin/Dexamethasone	10	9%	9	7%	0.2
Dexamethaosone alone	25	23%	18	14%	
VAD	9	8%	17	14%	
Alkylator-based	9	8%	6	5%	
Other	7	7%	2	2%	
Undetermined (excluded from p)	12	11%	24	19%	0.08
Response Prior					
CR/sCR/VGPR	22	21%	14	11%	0.06
PR	52	49%	75	60%	
MR (minimal response)	5	5%	9	7%	
NR/PD/SD	26	24%	22	18%	
Unknown	2	2%	5	4%	
Disease Status at transplant					
First Remission Consolidation	67	63%	76	61%	0.7

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	Case N=107		Control N=125		*P**
Primary Refractory	16	15%	18	14%	
Relapse: Sensitive	7	7%	13	10%	
Relapse: Refractory	9	8%	11	9%	
Relapse: Untreated	5	5%	3	2%	
Untreated	2	2%	1	1%	
Unknown	1	1%	3	2%	
Preparative regimen					
Melphalan alone	77	72%	89	71%	0.9

Abbreviation: auto-HCT, autologous Hematopoietic Stem Cell Transplantation; IMId, immunomodulatorydrug; VAD, Vincristine, Doxorubicin, Dexamethasone; CR, complete remission; sCR, Stringent Complete Remission; VGPR, Very Good Partial Response; PR, partial response; MR, minimal response; NR, no response; PD, progressive disease; SD, stable disease

*P value estimated on subsets of patients with known values

Table 2

Hepatitis B virus serologies in resolved infection group

	N = 107 (%)
HBcAb +	108 (100)
HBsAg +	0 (0)
HBsAb +	52 (49)
HBV DNA detectable	24 (22)
<100 IU/ml : 22	22
<300 IU/ml: 2	2
HBeAg +	0
Pre-emptive anti-viral Rx pre auto-HCT (Lamivudine)	1 (0.9)
Anti-viral Rx at reactivation (Lamivudine, Tenofovir)	4 (3.7)

Abbreviations: HbcAb+, Hepatitis B core antibody; HBsAg+, Hepatitis B surface antigen; HBsAb+, Hepatitis B surface antibody; HBeAg, Hepatitis B e antigen; auto-HCT, autologous Hematopoietic Stem Cell Transplantation; Rx, treatment

Table 3

Outcomes of the cases and controls

		Case N=107		Control N=125		HR	95% CI	*P*
Follow up in surviving patients, median (range), months		**18**	(0.2–136)	**35**	(0.6–168)			
NRM								
1 yr		1%	(0–7)	7%	(3–13)	0.15	0.02–1.2	*0.08*
2 yrs		1%	(0–7)	8%	(4–14)	0.13	0.02–1.1	*0.06*
Median OS		53m		67m				
1 yr OS		88%	80–93	87%	79–92	0.9	0.4–1.97	*0.8*
2 yrs OS		84%	74–90	75%	66–82	0.6	0.3–1.2	*0.2*
Median PFS		21m		18m				
1 yr PFS		68%	58–77	68%	59–76	0.9	0.6–1.6	*0.9*
2 yrs PFS		44%	33–55	40%	30–49	0.9	0.6–1.3	*0.5*
Incidence of HBV reactivation		n=7/107						
100 days		0%						
1 yr		3.5%	(1–11)					
2 yrs		5%	(2–13)					
Time to reactivation (median, range)		**16 m**	(7–47)					
Hepatotoxicity		***n=102***		***n=113***				
	0	26		37				
	1	52		54				
	2	16		16				
	3	8		6				
% Cumulative incidence >=2		30%	(21–43)	22%	(15–33)	1.3	0.7–2.3	*0.4*

Abbreviations: NRM, non relapse mortality; OS, overall survival; PFS, progression free survival; HBV, Hepatitis B Virus

*All outcomes are measured since autologous transplant, except for hepatotoxicity, where cumulative incidence measured since preparative regimen start date. Death before toxicity is considered competing risk

Table 4

Predictors of overall survival

	HR at 2 yrs	95% CI	P
Case	0.6	0.3–1.2	0.2
Control			
Gender			
Female	0.7	0.4–1.4	0.3
Male			
Diagnosis to TP>12 m	1.4	0.7–2.6	0.3
Age			
Qrt1 (31–51)	Ref.		
Qrt2 (52–58)	0.75	0.3–1.7	0.5
Qrt3 (59–63)	0.7	0.3–1.6	0.5
Qrt4 (64–75)	0.9	0.4–2.2	0.9
>=65 yrs	1.05	0.4–2.5	0.9
Disease Status at transplant			
First Remission Consolidation	Ref.		
Primary Refractory	2.3	1.02–5.3	0.04
Relapse	3.4	1.7–6.8	0.001
Untreated	excluded		
Unknown	excluded		
First Remission Consolidation	0.3	0.2–0.6	
Prep regimen			
Melphalan alone	0.5	0.3–0.9	
Cytogenetics			
Standard	Ref.		
High Risk	4.03	1.7–9.3	
Unknown	excld		
Serum creat at dx>2mg/dl	0.9	0.3–2.3	0.8
Induction			
Conventional	Reference		
New	0.8	0.4–1.6	0.6
Undetermined	1.9	0.9–4.3	0.1
Liver toxicity >=2 as time dependent variable (measured since prep start)	1.4	0.8–2.3	0.2
Reactivation in cases	7.4	0.8–69	0.08
Viral load in cases			
Detected	1.1	0.1–18	0.9
Undetected	Ref.		
Unknown	excld		

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